

Chapter 5: Chemical Mixtures

5.1 Introduction

The first step in characterizing risk posed by CERCLA sites is to compare estimated exposure intakes with toxicity values for each chemical of potential concern. This determines the likelihood of adverse effects in potentially exposed populations. Risk characterization is done separately for carcinogenic and noncarcinogenic effects because organisms respond differently to exposure from carcinogenic and noncarcinogenic agents (USEPA, 1989; 1990).

For carcinogens, a non-threshold dose-response model is used to calculate a cancer slope factor (the slope of the dose-response curve) for each chemical. EPA uses the linearized, multistage dose-response model in deriving the slope estimates. This model assumes that the dose-response relationship is linear in the low end of the curve (i.e., that the slope factor is a constant and risk is directly proportional to exposure intake).

For noncarcinogens, toxicologists recognize the existence of a threshold of exposure below which there is likely to be no appreciable risk of adverse health impacts. CERCLA guidance documents recommend comparing the estimated exposure intake to the reference dose (RfD) of each chemical of concern (USEPA, 1986a; 1986b; 1989). The RfD is defined as an estimate (with uncertainty spanning an order of magnitude or more) of a daily exposure level for human populations, including sensitive sub-populations, that is likely to be without an appreciable risk of adverse effect over the period of exposure (USEPA, 1989). RfDs are derived in toxicological studies from no-observable-adverse-effects levels (NOAELs) or from lowest-observable-adverse-effects levels (LOAELs), and the application of uncertainty and modifying factors (USEPA, 1989). The ratio exposure intake/RfD is termed the “hazard quotient” (HQ). Unlike the cancer slope factor, the hazard quotient is not a probabilistic measure of risk, but an indicator of the potential for adverse health effects.

Statistical studies performed by the EPA revealed that CERCLA sites contain hundreds of chemicals of potential concern in various media (USEPA, 1990). During a CERCLA risk characterization, assessors base the level of risk to human health from exposure to a multitude of chemicals on the toxic or carcinogenic properties of the individual components in the mixture. This is done because available toxicological data are not sufficient to derive RfDs for the chemical mixtures as a whole (USEPA, 1986a).

When little or no quantitative information is available on the potential interaction among the components in a chemical mixture, EPA recommends dose additivity (USEPA, 1986a; 1989; 1992). For carcinogens, the assumption of a linear dose-response relationship results in the calculation of a total carcinogenic risk by simply adding the estimated carcinogenic risk for each substance of concern. For noncarcinogens, the assumption that there is an identifiable exposure threshold below which there are no observable adverse effects results in the calculation of a hazard index (HI) by adding the hazard quotients of the substances that produce similar toxicological effects. Various concerns have been expressed about this methodology (Murphy, 1983; USEPA, 1992).



This chapter provides an overview of the use and evolution of the chemical mixtures methodology, the associated statutes and regulations from which this methodology derives, and issues associated with this methodology that are open to interpretation.

5.2 Discussion of Chemical Mixtures in EPA Guidelines

5.2.1 Guidelines for the Health Risk Assessment of Chemical Mixtures

The Guidelines for the Health Risk Assessment of Chemical Mixtures (USEPA, 1986a) were published to guide analysis of information relating to health effects data on chemical mixtures. The guidelines reflect the work initiated in January 1984, peer-reviewed by industry, environmental, and university groups, and published for public comment on January 9, 1985, [50 FR 1170] under the title Proposed Guidelines for the Health Risk Assessment of Chemical Mixtures.

The guidelines define “mixtures” as “any combination of two or more chemical substances regardless of source or of spatial or temporal proximity.” The examples given for mixtures include by-products from a single source or process (e.g., coke oven emissions, diesel exhaust), commercial products (e.g., PCBs, gasoline, pesticide formulations), and substances that come in contact after disposal or storage in the same area. The guidelines single out the final group of substances because (1) most instances of environmental contamination involve concurrent or sequential exposures to a mixture of compounds that may induce similar or dissimilar effects over exposure periods ranging from short-term to lifetime, and (2) there are uncertainties inherent in predicting the magnitude and nature of toxicant interactions, therefore no single approach can be recommended for application to risk assessments involving multiple chemical exposures.

The guidelines recommended that assessment of chemical mixtures is best conducted using toxicologic data on the specific mixture of concern or a reasonably similar mixture. However, if no data are available on the mixture of concern (a common situation), the risk assessment may be based on the toxic or carcinogenic properties of the individual components in the mixture. For systemic toxicants, the guidelines state that the methodology used by the EPA results in the derivation of a hazard index (HI) based on an exposure level that is not anticipated to cause significant adverse effects. The exposure levels are expressed as acceptable daily intakes (ADIs) or as reference doses (RfDs). For carcinogens, whenever linearity of the individual dose-response curves has been assumed, the increase in risk caused by an exposure is related to the carcinogenic potency.

The guidelines remark that the assumption of dose addition only applies to compounds that induce the same effect by similar modes of action, and that a separate HI should be generated for each end point of concern. For carcinogens, addition of individual risks assumes independence of action by the various carcinogens in the mixture. The guidelines note that most risk assessments are based on an assumption of dose additivity, as long as the components elicit similar effects, and that the methodologies used do not incorporate any form of synergistic or antagonistic interaction. If the compounds in a mixture do not have the same mode of toxicologic action, the guidelines recognize that dose additivity is not “the most biologically plausible approach,” and “can lead to substantial errors in risk estimates if synergistic or antagonistic interactions occur.”



5.2.2 Guidelines for Estimating Exposures

The Federal Register of September 24, 1986, published the EPA Guidelines for Estimating Exposures (USEPA, 1986b), as well as the responses to comments by the public and the EPA Scientific Advisory Board (SAB) on the guidelines. The guidelines provide EPA with a framework for performing exposure assessments. Before the guidelines became final, some commentors thought more discussion was necessary on the effect of chemical mixtures and potential synergistic effects on exposure. EPA answered by recognizing the need for further research in the area of exposure to chemical mixtures.

5.2.3 Superfund Public Health Evaluation Manual (SPHEM)

SPHEM (USEPA, 1986c) provided detailed guidance on how to conduct a public health evaluation at a Superfund site. Regarding chemical mixtures, SPHEM noted that for noncarcinogens, assessors compare estimated exposure intakes (E) to toxicological reference levels (RL). A hazard index (HI) is then calculated and is expressed as:

$$HI = \frac{E_1}{RL_1} + \frac{E_2}{RL_2} + \frac{E_i}{RL_i}$$

SPHEM indicated that the HI approach developed to assess the overall potential for noncarcinogenic effects posed by multiple chemicals assumes the following:

- multiple exposures to chemicals below their thresholds could result in an adverse effect, and
- the magnitude of the adverse effect will be proportional to the HI.

In addition, SPHEM required that assessors determine a subchronic HI and a chronic HI and that they evaluate the possible effects of multimedia exposure, which is estimated by summing the HIs for inhalation and oral exposures at each exposure point.

For carcinogens, assessors calculate risk by combining estimated exposure intakes with carcinogenic potency factors. SPHEM indicated that for carcinogens, risks are estimated as probabilities. Because “relatively low intakes are most likely from environmental exposures, it can be assumed that the dose-response relationship will be in the linear portion of the dose-response curve.” SPHEM remarks that the carcinogenic risk estimate will generally be an upper-bound estimate. Cancer risk additivity is based on the following assumptions delineated in SPHEM:

- The compounds involved act independently (i.e., there is no synergism or antagonism).
- Intakes of the individual carcinogens are small.

5.2.4 Risk Assessment Guidance for Superfund, Volume I [RAGS]

RAGS (USEPA, 1989) constitutes the present conceptual framework for CERCLA risk assessments. This guidance provides the current definitions for the following terms:

- Slope Factor: A upper-bound estimate of the probability of developing cancer per unit intake of a chemical over a lifetime. This value represents a 95-percent probability of developing cancer.
- Hazard Quotient (I-IQ): The ratio of a single substance exposure level to a reference dose for that substance. The exposure level and reference dose should have similar exposure periods (e.g., subchronic).
- Hazard Index (HI): The sum of the HQs for multiple substances and/or multiple exposure pathways. It is calculated separately for chronic, subchronic, and short-term exposures.

RAGS requires CERCLA risk assessments to evaluate the total risks to human health posed by a CERCLA site. The evaluation involves quantification of risks for each exposure pathway and quantification of site risks. The first step is accomplished by quantifying the cancer risk and hazard quotient for each substance of concern, and then summing the results to get the total cancer risk and hazard index for each exposure pathway. The second step involves combining risks across exposure pathways that affect the same individual over the same period of time. This is accomplished by summing the cancer risks and the hazard indexes.

The first step, quantification of risks for each exposure pathway, is delineated in RAGS under the section “Aggregate Risks for Multiple Substances.” Although the calculation procedures differ for carcinogenic and noncarcinogenic effects, both sets of procedures assume dose additivity in the absence of information on specific mixtures. Calculating a total cancer risk for each exposure pathway involves summation of carcinogenic effects, which, according to RAGS, involves the following assumptions:

- Intakes of the individual carcinogens are small.
- The substances involved act independently (i.e., there are no synergistic or antagonistic chemical interactions).
- All substances produce the same effect (i.e., cancer),

RAGS recognizes that there are several limitations in the approach. The implications of these limitations will be discussed in the summary and conclusions section.

- Total cancer risk estimates might become “artificially more conservative” because cancer slope factors are upper 95th percentile estimates of potency, which are not strictly additive.



- The risk equation for multiple substances sums all carcinogens equally, giving as much weight to Class B or C as to class A carcinogens. Slope factors derived from animal data will be given the same weight as slope factors derived from human data.
- Two different carcinogens might not act independently,

To assess the overall potential for noncarcinogenic effects posed by more than one chemical, the hazard index approach assumes the following:

- Simultaneous exposures to several chemicals below their RfDs could result in an adverse health effect.
- The magnitude of the adverse effect will be proportional to the sum of the HQs.

RAGS also recognizes several limitations with this approach:

- RfDs are derived from a single point on the dose/response curve, and they do not take into account the shape of that curve, resulting in RfDs not exhibiting equal accuracy or precision and not being based on the same severity of effect. Therefore, the level of concern does not increase linearly as the reference dose is approached or exceeded.
- RfDs are based on critical effects of varying toxicological significance. That is, two chemicals may cause liver damage, but one chemical may produce liver damage that is irreversible while the other does not. RfDs are also based on varying levels of confidence that include different uncertainty adjustments and modifying factors.
- Assumption of dose additivity is most properly applied to compounds that induce the same effect by the same mechanism of action. If the HI is greater than unity as a consequence of summing several HQs of similar value, it may be appropriate to segregate the compounds by effect and by mechanism of action. Segregation of HIs requires identification of the major effects of each chemical, including those seen at doses higher than that causing the critical effect. Major effect categories include neurotoxicity, developmental toxicity, reproductive toxicity, immunotoxicity, and adverse effects by target organ (i.e., hepatic, renal, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, and dermal/ocular effects). ATSDR Toxicological Profiles are well suited in format and content to allow a rapid determination of additional health effects that may occur at exposure levels higher than those that produce the critical effect.

The final step, quantification of site risks, is delineated in RAGS under the section “Combining Risks Across Exposure Pathways.” RAGS states that “the total exposure to various chemicals will equal the sum of the exposures by all pathways.” According to RAGS, the following steps assure the appropriateness of combining cancer risks or HIs to get the total site risk



1. Identify reasonable exposure pathway combinations. For each pathway, cancer risks and HIs are developed for particular exposure areas and time periods. If two pathways do not affect the same individual or subpopulation, neither pathway's individual cancer risk estimate or HI affects the other, and they should not be combined.
2. Examine of the likelihood that the same individuals would face the RME by more than one pathway. Because contaminant concentrations vary over time and space, the same individual may not experience the RME for more than one pathway over a certain period of time. Combining the RME risks for more than one pathway may be done if it is explained why the key RME assumptions for more than one pathway apply to the same individual or subpopulation.

5.2.5 Guidelines for Exposure Assessment

These guidelines (USEPA, 1992), published in response to recommendations from EPA's SAB and the general public, superseded and replaced the Guidelines for Estimating Exposures (USEPA, 1986b) and Proposed Guidelines for Exposure-Related Measurements (USEPA, 1988). The guidelines convey the principles of exposure assessments and constitute the current theoretical principles to be used in the Superfund program. The central theme of the document is to find "a more realistic approach to exposure determination." The guidelines suggest that "since risks resulting from exposures to complex mixtures of chemicals with the same mode of toxic action are generally treated as additive in a risk assessment, failure to evaluate one or more of the constituents would neglect its contribution to the total exposure of risk."

5.2.6 An SAB Report: Superfund Site Health Risk Assessment Guidelines

This SAB report (USEPA, 1993) was published as a result of an SAB meeting held on April 7-8, 1992, in Bethesda, Maryland. The meeting was organized to review key issues related to RAGS. One of these issues was how to assess and deal with exposures to multiple chemicals using the hazard index (HI)/hazard quotient (HQ).

The SAB committee was asked the following specific questions:

1. Is it appropriate to add risk estimates for multiple contaminant exposures (i.e., to calculate HI for noncarcinogenic chemicals with similar toxic endpoints, and simple additivity of cancer risks)?
2. Is it appropriate to use an HI greater than 1 as a threshold of concern?
3. What does an HI greater than 1 represent when the HQs used to calculate the HI are individually less than 1?
4. Is the RfD an appropriate criterion of toxicity?



In answering the first question, the SAB committee remarked that there is concern about the approach of using an RfD derived HI/HQ as a basis for adding risks from exposures to complex mixtures because the RfD is only an indirect index of potency. The EPA HIs depend upon RfDs, which in turn, depend upon effect levels (e.g., NOAEL) divided by an uncertainty factor. The SAB notes that potency should be defined by the form of the dose-response relationship, not by a single point on the dose-response function.

In relation to the second question, the SAB committee stated that an HI equal to unity has a rational and meaningful basis for defining a threshold of concern, but the committee “does not see any value to use numbers other than ‘1’ in defining a threshold of concern.” The SAB comments that the HI approach is not based upon a linear dose-response relationship and that using the HI may even be “inappropriate if there are interactions of the chemicals in the mixture which cannot be fully characterized by a combination of dilution-type interaction and independent mechanisms of action.”

To answer the third question, the SAB committee indicated that the interpretation of an HI greater than unity may be based on several factors:

- If two or more agents involved share the same mechanism of toxicity, their doses could well be additive.
- If they act upon two or more sites, they could be supra-additive,
- If they each act by different toxicological mechanisms, additivity of risks for a common endpoint is not necessarily to be expected.

The SAB recommends considering that there is a potential increase of risk when the HI exceeds unity. However, the committee warns that without a more complete understanding of interaction mechanisms, there cannot be a statement of how rapidly this increase occurs.

Finally, the SAB noted that if experimentally determined RfDs for specific mixtures were available, then the HQ of the mixture would be an indication of risk relative to the RfD. Currently, chemicals in a mixture are assessed for joint action by computing the ratio of exposure to RfD, then adding these quotients to obtain the HI. According to the SAB, comparisons of HQs for different agents are not meaningful. Because the RfDs are based on dose such as NOAELs that are derived from the critical effect in an assay, the resulting HI may encompass a spectrum of toxic endpoints and risk levels.

5.3 Issues and Regulator Dialogue

5.3.1 Chemical Mixture Issues

To perform CERCLA risk assessments, assessors must evaluate quantitative relationships between exposure and the effects in the studies to identify which effects are of concern, i.e., dose-response assessments. However, toxicological information on specific mixtures found at CERCLA sites is rarely



available, and even if such data existed, monitoring for mixtures or modeling the movement of mixtures across space and time present technical problems (USEPA, 1989). One scientific paper suggested toxicological procedures that “may be performed to evaluate whether a significant health risk is posed by exposure of men to a mixture of chemicals that may be present because of improper chemical waste disposal practices.” This paper concluded that “with current techniques and the present state of knowledge, there is no ideal way of approaching the problem of assessing the toxicity of exposure of man to mixtures of chemicals; it is a goal which will not be obtainable in the foreseeable future” (Neal, 1983).

If sufficient data are not available on the effects of the chemical mixture, the current approach is to assume dose additivity. For carcinogens, simple additivity of risk is used; for noncarcinogens, an HI approach was developed where there is concern for potential adverse effects if the sum of the hazard quotients for several chemicals with the same toxic endpoint exceeds unity. Dose additivity, however, introduces uncertainties into the risk assessment. The following issues were identified:

Dose Additivity Can Lead to Errors If Synergistic or Antagonistic Interactions Occur

In addition to considering the contributions of individual agents, assessors must also consider the combined effects of agents present, taking into account the modes of action, when known, of the organs or systems affected; the possible joint severity of the effects; all and any synergism or antagonism that may be present (USEPA, 1992). Dose additivity is based on the assumption that the components in the mixture have the same mode of action and elicit the same effects and have independent mechanisms of action (meaning that the thresholds for a given chemical are unaffected by exposures from other chemicals) (USEPA, 1993).

A “toxicological interaction” may be defined as a condition in which exposure to two or more chemicals results in a quantitatively or qualitatively altered biological response relative to that predicted from the action of a single chemical (Murphy, 1983). Since the mechanisms of action for most compounds are not well understood, the justification of the assumption of dose addition will often be limited to similarities in pharmacokinetic and toxicological characteristics (e.g., apparent target organ). According to EPA, several commentators have expressed concern that it was difficult to define sufficient similarity and that the guidelines should give more details concerning similar mixtures. EPA agreed with the comments, but indicated that “the best indicators of similarity in terms of risk assessment are yet to be determined [51 ER 34014].

If some of the chemicals interact synergistically, then the condition $HI = 1$ may not afford adequate protection. On the other hand, if the individual chemicals have independent mechanisms of action, then the criterion $HI = 1$ may be overly protective. The Guidelines for the Health Risk Assessment of Chemical Mixtures (USEPA, 1986a) state in this respect that “dose additive models are not the most biologically plausible approach if the compounds do not have the same mode of toxicologic action,” and that “additivity can lead to substantial errors in risk estimates if synergistic or antagonistic interactions occur.”

Summing HQs Treats All RfDs Equally

The EPA is currently addressing the appropriateness of RfDs as a criterion of toxicity (USEPA, 1993). The concept of RfD was first published in Reference Dose (RfD): Description and Use in Health Risk Assessments (Barnes and Dourson, 1988). This paper describes EPA's approach and rationale to solve "perceived difficulties" with the concept of acceptable daily intake (ADI), safety factor, or margin of safety. The concept of reference dose was introduced "to avoid use of prejudicial terms (e.g., 'safety' and 'acceptable'), to promote greater consistency in the assessment of noncarcinogenic chemicals, and to maintain the functional separation between risk assessment and risk management" (Barnes and Dourson, 1988). The position paper delineates the scientific shortcomings and difficulties in utilizing the "traditional" approach:

1. A too narrow a focus on the NOAEL ignores the information on the shape of the dose-response curve.
2. There are questions about the selection of the appropriate adverse effect.
3. There is a lack of guidelines to address the reliability of toxicity studies due to the number of animals used.

Barnes and Dourson also note that the derivation of RfDs involves the use of uncertainty factors (UF) and modifying factors (MF) which depend upon the professional assessment of scientific uncertainties in the toxicological studies (e.g., the completeness of the overall data base and the number of species tested). The following factors are used in deriving an RfD:

1. 10-fold factor to account for the variation in sensitivity among human populations,
2. 10-fold factor to account for the uncertainty involved in extrapolating from animal data to humans,
3. 10-fold factor to account for the uncertainty involved in extrapolating from less than chronic NOAELs to chronic NOAELs,
4. 10-fold factor to account for the uncertainty involved in extrapolating from LOAELs to NOAELs, and
5. use of professional judgment to determine the MF (it is greater than 0 and less than or equal to 10).

Because each RfD is based on a critical effect (e.g., NOAEL, LOAEL), the resulting sum of HQs (i.e., the HI) contains a spectrum of toxic endpoints (e.g., death, weight-loss, skin rashes, etc.). Also, the addition of RfDs includes adding data sets with disparate levels of confidence.



Cancer-causing Substances are Treated Equally When Summing Slope Factors

EPA evaluates available toxicological data from experimental animals and from epidemiological studies of human populations to determine the carcinogenicity of chemical substances. Based on the amount and type of the data available, EPA assigns a weight-of-evidence classification. The addition of slope factors for multiple chemicals in a mixture sums all carcinogens equally, regardless of their carcinogenicity classification (see Chapter 1 for the classification scheme).

Upper 95th Percentile Estimates of Potency Are Not Strictly Additive

The dose-response curves from animal toxicological experiments are based on data sets derived from high administered doses. The estimation of a slope factor at the low end of the dose-response curve requires extrapolation of the data set to lower exposure levels. There are various mathematical models that have been developed to extrapolate from high to low response doses (e.g., linearized multistage model, Weibull, probit, logit, one-hit, etc.) The choice of an extrapolation model is outlined in Guidelines for Carcinogen Risk Assessment (USEPA, 1986d). The guidelines recommend fitting the experimental data set to the linearized multistage model which assumes that the low-end portion of the dose-response curve is linear. The carcinogenic slope factors published by EPA are the slopes of these curves calculated as an upper 95th percentile confidence limit of the probability that a chemical will cause cancer. It has been mathematically proven that the product of 95th percentiles will result in “compounding conservatism” (Taylor, 1993). RAGS notes that when adding cancer slope factors from multiple chemicals, “the total cancer risk estimate might become more conservative” (USEPA, 1989).

5.3.2 Regulator Dialogue

Review of CERCLA guidance documents revealed that various assumptions are made to determine the levels of risk to human health from exposures to multiple chemicals. According to SPHEM, the results for multiple chemicals “should not be interpreted too strongly,” and the interpretation of the HI for a particular site requires the use of professional judgment (USEPA, 1986c). Because of the uncertainties involved in toxicological effects of chemical mixtures, the guidelines recommend a thorough discussion of all assumptions in the assessment of health risk from chemical mixtures.

As discussed previously, there is a great deal of uncertainty involved in adding HQs. One method that can be used to reduce this uncertainty, which is also recommended in the guidance documents, is to calculate an HI for each affected target organ. The HQs for chemicals that affect different target organs should not be summed for one or multiple exposure pathways. The IRIS database and HEAST specify which target organ is affected (critical effect) by a substance when the RfD value is presented.

Uncertainties are also introduced into the risk assessment if risks from carcinogenic chemicals with different weight-of-evidence values are summed. The only known human carcinogens are Group A chemicals. The other groups’ risks are based mostly on animal studies, with their inherent uncertainties for predicting human carcinogenicity. Situations could exist where a less extensive and costly remedial alternative may be chosen based on cancer risks summed only within the same weight-of-evidence classification, while another more extensive and costly alternative might be required based on risks



associated with summed cancer risk, regardless of their weight-of-evidence classification. However, even when summing carcinogens with the same weight-of-evidence classification, the result will be conservative because the slope factors are 95th percentiles, which, as seen in the previous section, are not strictly additive. Thorough description of such issues in the uncertainty section of the risk assessment will present the remedial decisionmaker with insight that could bear significantly on the remedial selection process.

EPA and ATSDR are currently developing and supporting research programs designed to gain an understanding of the mechanisms of interactions to predict how specific mixtures of toxicants will interact. The ATSDR is under U.S. congressional mandate to conduct health assessments at all National Priority List (NPL) sites, including federal facilities. A Memorandum of Understanding (MOU) between ATSDR and the Department of Energy (DOE) describes the role ATSDR plays at DOE sites, including the preparation of toxicological profiles for substances requested by DOE (MOU, 1991). CERCLA Sections 104(i) (3) and (5) also mandate the preparation of toxicological profiles by ATSDR to support CERCLA activities.

DOE may appropriately decide to sponsor toxicological studies for a particular chemical mixture that is present at various DOE facilities. The time and money spent on the toxicity study may well be worth the effort if the results of the study can reduce the risk and uncertainty of simply adding the HQs of the individual chemicals in the mixture. The following initiatives were suggested to determine how the risk of exposure to a mixture compares to the risk from exposure to each chemical alone (Murphy, 1983):

1. search existing literature for laboratory, clinical, or epidemiological studies that deal with exposures to the combination of chemicals;
2. initiate laboratory or epidemiological studies to test for interactive effects of the specific combination of chemicals; and
3. use toxicokinetic and toxicodynamic characteristics of individual chemicals to predict potential for altered health risks arising from exposure to mixtures.

There are few reports of laboratory or epidemiological studies, however, that have addressed the toxic interactions of chemical mixtures, particularly from mixtures that might arise from a chemical waste dump. Comprehensive toxicological testing of the combination of chemicals to which humans may conceivably be exposed is of "Herculean proportion" (Murphy, 1983). Thus, it is necessary to consider the basic principles underlying the mechanisms of toxic interactions in order to predict the effects of chemical mixtures. The scientific paper concludes that predicting the likelihood of increased risk due to multichemical exposures requires detailed information concerning each of the components. Assessors should perform a structure activity relationship (SAR) analysis on the individual chemicals in the mixture before initiating expensive testing.

5.4 References

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